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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,564	11/30/2001	Andre Lieber	30429-2USWO	8863

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

FL

Office Action Summary	Application No.	Applicant(s)	
	09/980,564	LIEBER ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2004*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *121-145* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *121-145* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.D

DETAILED ACTION

This office action is in response to an amendment filed 4/29/05 and 5/19/05. Claims 1-120 have been cancelled. Claims 121 and 122 have been amended. Claims 121-145 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 May 2005 has been entered.

Drawings

The drawings are objected to because the packaging signal that should be in Figure 17A, last vector and was found in the original drawing is missing and not indicated as deleted in the marked up figure. Appropriate correction is required.

Specification

The amendment filed 4/29/05 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: applicants have amended page 10, beginning at line 14 to state that in 17A, the IRs are 1.2kb and that the "lower" vector comprises the "same" IRs.

Furthermore, on page 86 beginning at line 10, the specification has been amended to recite that pCD1 is depicted in figure 9. However, pCD4 is depicted in Figure 9.

Applicant is required to cancel the new matter in the reply to this Office Action.

The disclosure is objected to because of the following informalities: on amended page 86, the last sentence prior to the description of 17B, appears to be a sentence fragment. It states "Recombination between IRs shown on the left side generates at the left f", which fragment is not followed by a period.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 121-145 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 11/2/04 and restated below.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a

conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The instant invention is drawn to a recombinant double-stranded adenovirus vector comprising a parallel DNA strand and an anti-parallel DNA strand and three sets of inverted repeat sequences; 1) adenovirus ITR, 2) AAV ITR and 3) an unrecited source of IRs, and a heterologous promoter and a foreign gene sequence. The antiparallel strand of the recombinant adenovirus double-stranded DNA encodes a modified adenoviral fiber protein. The invention utilizes disciplines of molecular biology, cell biology and viral biology.

2) Scope of the invention. The adenoviral vector of the instant invention is designed to incorporate characteristics of several systems. The vector has altered or directed tropism for desired target cells by virtue of the modified fiber. Also the vector can integrate into a host cell chromosome based upon inclusion of the AAV ITR sequences. Finally, the inverted repeats appear to be used to generate a gutless vector by homologous recombination in which the surrounding adenoviral genome is recombined out of the vector. Each goal alone is complex and requires great skill in the art.

3) Number of working examples and guidance. The disclosure provides guidance for the generation of hybrid adenoviral vectors that have AAV ITR sequences and foreign genes under control of heterologous promoters inserted into an adenoviral vector. The disclosure provides further guidance for alteration or modification of the fiber proteins. The fiber proteins are truncated or deleted and replaced with fiber sequences (see page 83-86 which describes the

generation of Ad5GFP/F35) from other serotypes or ligand peptide sequences are inserted into the fiber coding sequences (see page 95-98 which describes insertion of ligands into GH loops).

4) State of Art. The specification defines parallel and anti-parallel strands of DNA as referring to each of the strands of DNA of the double stranded adenovirus. Specifically, the anti-parallel strand of DNA is said to refer to the other of the two strands of DNA, which is not depicted in accompanying figures.

In contrast to the instant disclosure, the art does not teach that the double-strands of adenovirus DNA are referred to as parallel and antiparallel. Rather a review of the art has demonstrated that the strands of DNA are more commonly referred to as "r" and "l" strands and DNA in general is often referred to as comprising "sense" and "antisense" strands (see e.g. Hitt, Advances in Pharmacology page 139). Given the art and specification derived definitions, it appears that the parallel strand of the instant invention corresponds with the art defined "r" strand while the antiparallel strand corresponds to the "l" strand.

The specification also states that the fiber protein is encoded on the anti-parallel strand of DNA (page 19, line 24-30). Specifically, from the disclosure it appears that the fiber protein is produced by transcription in a 5' to 3' direction of what corresponds to the "l" strand. However, the art teaches that the fiber protein is encoded by the r-strand of the adenovirus genome or the top strand (see e.g. Hitt, Advances in Pharmacology page 139). Adding to the confusion of the terminology depicting the location of the fiber protein, the specification describes fusion of the ad35 knob and shaft to the tail region of ad5 fiber coding sequences (page 85, which is illustrated in figure 18). The modified fiber protein in figure 18 shows that the coding sequences are from

base 30,598 to base 32,781. Therefore, it appears here that the "parallel" strand encodes the fiber protein.

5) Unpredictability of the art. The development of adenoviral vectors for gene therapy is a complex art that requires great skill in the art furthermore, modification of the integrative ability **and** the tropism of the vector simultaneously requires a complex series of manipulations of the adenoviral genome. The instant recombinant double-stranded adenovirus vector comprising a parallel DNA strand and an anti-parallel DNA strand and three sets of ITR sequences from adenovirus, AAV and an unrecited source as well as an "antiparallel strand" that encodes a modified adenoviral fiber protein, which alters the tropism of the adenovirus vector, requires modifications of the adenoviral genome that are highly unpredictable given the lack of guidance in the instant specification.

Specifically, applicants recite that the fiber protein is encode by the "antiparallel" strand of the double stranded DNA. This configuration is not possible given the known genomic organization of adenovirus, which teaches that transcription of the adenovirus vector in a 5' to 3' direction on the upper strand produces the fiber protein mRNA. Therefore, the specification has not taught how the anti-parallel strand can be modified to express a modified fiber protein.

6) Summary. The invention recites a complex series of methods for the generation of a modified vector with altered tropism and that integrates into the host chromosome. The unpredictability of making the claimed invention is accentuated due to the lack of processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains andgiven that applicants have not exemplified the construction of a vector with a fiber protein on the

antiparallel strand, it would require undue experimentation to generate a vector with a fiber with altered tropism on the antiparallel strand: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument- 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 10-12 of the amendment filed 4/29/05. Applicants argue that the fiber sequence in its native location is not essential for expression of surrounding genes as demonstrated by the ability to delete it and still generate viral plaques. Applicants refer to Hitt et al which teaches that the fiber can be inserted into the E1 or E3 region as support that the fiber can be inserted into these regions. Applicants cite a separate example that purportedly teaches that the nucleotide sequence that mediates replication of an adenovirus in a transduced cell can be on the anti-parallel strand.

Applicants' arguments filed 8/12/04 have been fully considered but they are not persuasive. Applicants have not confirmed that the antiparallel and parallel strands, which art not art recognized terms for the viral strands, actually refer to what is commonly known in the art as the l strand and the r strand. The following arguments are made with the understanding that this the designations of parallel and antiparallel refer to l and r respectively. Claims 121-145 stand rejected because undue experimentation would be required of a person of skill in the art to generate the instantly recited vector. Applicants have argued that placement of the fiber on the

anti-parallel strand would not disrupt surrounding sequences because it has been demonstrated that the fiber coding sequences can be deleted without affecting the ability of the virus to form plaques. Firstly, the fiber is not necessarily deleted in this case, rather it is inserted elsewhere on the genome of the virus. Secondly, in order to generate a vector that has altered tropism, the fiber sequences would need to be expressed in a temporally and spatially restricted manner. Insertion of the fiber sequence into the E1 and E3 region would not place these sequences on the antiparallel strand. Nonetheless, should this arrangement be the goal, it would alter the spatial and temporal expression of this protein. It is not clear that expression of the fiber at the same time and spatially with the replication proteins would allow its incorporation into the particle. Given that applicants have not exemplified the construction of a vector with a fiber protein on the antiparallel strand, it would require undue experimentation to identify sites of insertion of the fiber protein such that its expression is spatially and temporally maintained for generation of a particle with altered tropism. It is noted that applicants have referred to a second example in Hitt that teaches that the nucleotide sequence that mediates replication of an adenovirus in a transduced cell can be on the anti-parallel strand. However, no such passage could be found.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

July 22, 2005

DANIEL M. SULLIVAN
PATENT EXAMINER